REMARKS

The Pending Claims

Claims 1, 4, 6-15, 18-20, 24, and 26, remain pending, claims 1, 4, 6, 7, and 9-15 have been withdrawn from consideration, and claims 2, 3, 5, 16, 17, 21-23, and 25 have been canceled without prejudice.

Claims 8, 24, and 26 have been amended to describe the invention more clearly. No new matter has been added, the basis for the amended claim language may be found within the original specification, claims and drawings. Entry of the above is respectfully requested.

The Office Action

For convenience, the following remarks will address the rejections in the same order they were raised in the Office Action.

Rejections under 35 USC 103

Claims 8 and 18-20 were rejected under 35 USC 103(a) as being unpatentable over NINDS, 1995 (*N. Engl. J. Med. 333*:1581-1587) in view of Bundick et al., 1992 (*Transplantation, 53*:1150-1153) and Mori et al., 1997 (*J. Immunol.* 158: 659-3665), and further in view of Sharkey et al., 1994 (*Nature, 371*:336-339) or Kelly et al., 1997 (U.S. Pat. No. 5,648,351) as evidenced by Steiner et al., 1998 (*Eur. Neurol., 40*:1-8).

Claims 21-26 were rejected under 35 USC 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al., 1992 and Mori et al., 1997, and further in view of Sharkey et al., 1994 or Kelly et al., 1997 as evidenced by Steiner et al., 1998, and further in view of Meden et al., 1993 (*J. Neurol. Sci.,* 119:219-216), and Hantson et al., 1997 (WO 97/15323).

Each of these rejections is separately and respectfully traversed.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness in regard to the present invention. One of ordinary skill in the art would not be led to modify the teachings of NINDS in the precise manner which yields the claimed invention.

As the Office Action correctly notes, NINDS does not teach combination therapy with t-PA and an IL-2 inhibitor. While Steiner et al. refers to the general idea of combination therapy with respect to neuroprotectants and thrombolytics, and speculates that combination therapy with neuroprotective and thrombolytic agents "<u>may provide</u> additional benefits" (Abstract, emphasis added), there is no disclosure in Steiner et al. (or in any of the other cited references) of using FK506 in combination with t-PA, and one of ordinary skill in the would not be led from the cited references to this combination.

Moreover, as noted in the Office Action, Steiner et al. states that t-PA is "only approved by the FDA for the treatment of acute stroke within a 3-hour time window" (page 2, paragraph 2, emphasis added; *see also,* Meden et al. referring, as noted in the Office Action, to a two hour period). In contrast, claim 8, as presently amended, requires "administering the effective amount of t-PA and the effective amount of tacrolimus or its hydrate 3 hours after the occurrence of the cerebral ischemic disease and/or brain damage caused by ischemia" (emphasis added). Accordingly, even if one of ordinary skill in the art could be led from the speculative and general statements in Steiner et al. to the combination use of FK506 and t-PA, Steiner et al., in indicating the only approved treatment is within a 3-hour time window, would led one *away* from the claimed invention.

As demonstrated in the application, the effectiveness of administering the effective amount of t-PA and the effective amount of tacrolimus or its hydrate 3 hours after the occurrence of the cerebral ischemic disease and/or brain damage caused by ischemia is a remarkable advantage of the invention. As shown in Example 1 (page 16, line 22 of text, through page 17, line 4 of text):

> Additionally, when drugs were administered 3 hours after occlusion of the MCA, t-PA increased the brain damage (-13.8±7.0%). On the contrary, the combination of FK506 and t-PA caused the significant reduction of ischemic brain damage and its inhibition is 16.2±7.6%.
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> These results indicate that FK506 is able to decrease the serious damages caused by t-PA. In other word, the above results indicate that the combination of FK506 and t-PA not only prolongs the therapeutic time window but also produces increased efficacy and safety for treatment of the ischemic brain damage.

It is respectfully submitted that this showing of a surprising and synergistic effect further evidences the non-obviousness of the claimed invention.

Accordingly, even if: Bundick et al. and Mori et al. each disclose FK506 is an IL-2 inhibitor, and Sharkey et al. and Kelley et al. each disclose FK506 has neuroprotective activity, and Meden et al. discloses combination therapy including t-PA within 2 hours, and Hantson et al. discloses simultaneous or sequential treatment using a neuroprotectant and a thrombolytic agent, this is of no import. Bundick et al., Mori et al., Sharkey et al., Kelley et al., Meden et al., and Hantson et al., whether taken alone or in combination, do not cure the deficiencies of NINDS and Steiner et al. (and Steiner et al. and Meden et al. teach away from the present invention) and thus, the combination fails to render the present invention obvious.

Accordingly, since the cited art does not lead one of ordinary skill to the claimed invention, and in view of the synergistic effect and other advantages shown, it is respectfully submitted that the rejection cannot be maintained.

For the reasons set forth above, reconsideration of the rejections is respectfully requested.

Conclusion

In view of the amendment and remarks recited herein, the application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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